REMARKS

I. Support for the Amendments

Claims 1-21 were originally in the application. Claims 6-21 were canceled previously without prejudice or disclaimer of any subject matter.

Claims 1-5 and 22 are presently in the application. Claims 1 and 22 have been amended. No new matter has been added by virtue of these amendments.

Support for amended claims 1 and 22 can be found in the original specification and claims. Additional support for amended claims 1 and 22 can be found, e.g., on page 3, lines 3-22; on page 4, lines 1-4; from page 5, line 26, to page 6, line 7; on page 6, lines 16-20; from page 6, line 23, to page 7, line 25; on page 8 line 3-6; in Figures 1-3, 7, and 9-10; and in the Examples, particularly in Examples 1-3.

More specifically with respect to claim 1, additional support for the amendments to the preamble of claim 1 can be found, e.g., on page 3, lines 9-11; on page 5, lines 4-5 and 23-25; on page 6, lines 16-22; from page 6, line 28, to page 7, line 3; on page 12, lines 14-15; in Figures 1-3; and in the Examples, particularly in Example 3. Additional support for the amendments to step a of claim 1 can be found, e.g., on page 3, lines 16-18; on page 7, lines 3-9; and in the Examples, particularly in Examples 1-2. Additional support for the amendments to step b of claim 1 can be found, e.g., on page 3, lines 15-18; and in the Examples, particularly in Examples 1-3. Additional support for the amendments to step c of claim 1 can be found, e.g., on page 3, lines 11-12; on page 12, lines 10-11; in Figure 7; and in the Examples, particularly in Example 3. Additional support for the amendments to step d of claim 1 can be found, e.g., on page 3, lines 8-13; on page 12, lines 11-13; and in the Examples, particularly in Example 3. Additional support for the amendments to step e of claim 1 can be found, e.g., on page 6, lines 15-17; on page 12, lines 14-15; in Figures 1-3; and in the Examples, particularly in Example 3.

More specifically with respect to claim 22, additional support for the amendments to claim 22 can be found, e.g., on page 5, lines 23-28; from page 12, line 22, to page 13, line 2; in Figures 9-10; and in the Examples, particularly in Example 3.

II. Status of the Claims

Claims 1-21 were originally in the application. Claims 1-21 were subject to an election/restriction requirement, and claims 1-5 were elected with traverse. Claims 6-21 were canceled without prejudice or disclaimer of any subject matter.

Claims 1-5 and 22 are presently in the application. Claims 1 and 22 have been amended. No new matter has been added.

III. The Examiner's Remarks Concerning the Specification are Addressed

The Examiner has withdrawn the objections to Table 1 and SEQ ID NO: 51, based on the Amendment filed in March 2004, which returned H12 to the sequence originally filed. Applicants thank the Examiner for withdrawing these objections.

On page 2 of the Office Action, the Examiner states:

> In the previous response, altering the amino acid sequence of H12 from HLYQGOQW to HLYQGCQW (amendment filed 1-13-03 and again in the amendment filed 5-9-03) was found to be new matter because it was not readily apparent that "0" should have been "C" or that "W' should have been "W'. In applicants' response filed 3-15-04, H12 was amended back to HLYOGOQW as originally filed. Table 1 and SEQ ID NO:51 are no longer objected to. [P. 2.]

Applicants have withdrawn the amendments requested, but are concerned that their arguments may have been misunderstood. For the record, Applicants wish to note that their previous argument was as follows:

> Table 1 lists peptides synthesized based on the sequence of the human Her-2/neu protein wherein each sequence contained the anchor motif for HLA A2.1, that is, L, I, M, V, A, T at position 2 and position 8/9/10 (Rupert, J. *et al. Cell* (1993) 74:929-937). *See page 8, lines 25-27 of the specification.* The sequence corresponding with peptide H12 in Table 1 now reads "HLYQGCQVV". Those of skill in the art would recognize that as originally written, 'O' is not a standard abbreviation, that the sequence is too short, and that the sequence does not have L, I, M, V, A, T at position 8/9/10. The correct sequence is found in the Ruppert, *et al.* reference cited at page 8, lines 25-27 of the specification. Further, the Erb2 Human sequence (with Her2 and Neu listed as synonyms) was entered in Swiss-Prot and originally released on 05 August 1987. Still further, the c-erb-B-2 precursor (Homo sapiens) was available on-line on March 30, 1995. [Amendment, Jan. 6, 2003; emphasis in original.]

While "it was not readily apparent that "O" should have been "C" or that "W" should have been "VV," one of ordinary skill in the art would have recognized that the sequence presented was incorrect, based on the information within the specification itself and the state of knowledge at the time of filing, and would have been motivated to refer to the correct information, which was publicly available at the time when the application was filed.

Applicants nonetheless wish to thank the Examiner for withdrawing the objections to Table 1 and SEQ ID NO: 51, based on the Amendment filed in March 2004.

IV. Rejection of Claims 1 and 22 Under 35 U.S.C. §112, First Paragraph, is Traversed, but Accommodated

The Examiner has rejected claims 1 and 22 under 35 U.S.C. §112, first paragraph, "as failing to comply with the written description requirement." Applicants respectfully traverse the Examiner's rejection.

The Patent Office alleges:

> The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.
>
> The limitation "specific... ...for HLA restriction" in the preamble of claim 1 does not have support in the specification as originally filed. Support cannot be found on pg 3, lines 3-22, pg 4, line 1-4, pg 5, line 26, through pg 6, line 7; pg 6, lines 16-20, pg 6, line 23-pg 7, line 25, pg 8, line 3-6, Fig. 13, or the Examples. [Pp. 2-3.]

Applicants respectfully traverse the rejection, but have amended the preamble of claim 1 in the interest of speeding prosecution, both with respect to the Examiner's remarks under §112, first paragraph, and with respect to the Examiner's remarks under §112, second paragraph. As noted, *supra*, additional support for the amendments to the preamble of claim 1 can be found, e.g., on page 3, lines 9-11; on page 5, lines 4-5 and 23-25; on page 6, lines 16-22; from page 6, line 28, to page 7, line 3; on page 12, lines 14-15; in Figures 1-3; and in the Examples, particularly in Example 3.

Lines 9-11 on page 3 describes a non-human TCR which "is human HLA-restricted and specific for a tumor-associated antigen." A similar description can be found on page 5, lines 4-5 and 23-25 and from page 6, line 28, to page 7, line 3. Figures 1 and 2 (see also page 6, lines 16-22) provides examples of single chain TCR's (scTCRs) show patterns for construction of relevant plasmids embodying the present invention. The complete sequence for one of the single-chain TCRs generated by the method of the present invention is shown in Figure 3 (see also page 8, lines 9-10). These procedures were used in Example 3, along with the genes encoding the relevant α and β chains of the TCRs specific for H3, H7, and p53.

Figure 9 (see also Example 3) shows the results of an assay in which H7 dimer and H7 scTCR of the present invention were transfected into 27J cells, which were exposed to JA^2 cells with or without H7 peptide. Only 27J cells transfected with H7 dimer or H7 scTCR exposed to JA^2 cells with H7 responded by producing IL-2.

Figure 10 (see also Example 3) shows the results of a similar assay in which the transfected 27J cells produced IL-2 in response to HER2/neu-derived peptides and cells presenting HER2/neu peptides.

With respect to step c of claim 1, the Patent Office alleges:

> The limitation of "cloning or amplifying said nucleic acid molecule comprising a nucleotide sequence isolated from the HLA restricted CTL and encoding..." in claim 1, step c, does not have support in the specification as originally filed. Example 3 teaches cloning α and β chains of TCRs found in CTL recovered from mice that had been administered peptides (starting on pg 12, line 10; see pg 13, line 1). Claim 1, step c, encompasses cloning one molecule that encoding both the α and β chain and cloning a portion of a TCR that comprises an α/β chain variable region without cloning the α/β chain variable region itself. [P. 3.]

Applicants respectfully traverse the rejection, but have amended step c of claim 1 in the interest of speeding prosecution, both with respect to the Examiner's remarks under §112, first paragraph, and with respect to the Examiner's remarks under §112, second paragraph. As noted *supra*, additional support for the amendments to step c of claim 1 can be found, e.g., on page 3, lines 11-12; on page 12, lines 10-11; in Figure 7; and in the Examples, particularly in Example 3.

In addition to the language of lines 11-12 on page 3 and lines 10-11 on page 12, the Examiner's attention is respectfully directed to the sequence of Figure 7 (see also Example 3), which shows sequence recovered from transgenic mice, which had been administered H7 peptide.

With respect to step e of claim 1, the Patent Office alleges:

> Fusing any "recovered TCR receptor encoding nucleic acid molecules together to prepare the isolated fused nucleic acid molecule" (claim 1, step e) does not have support in the specification as originally filed. Example 3, pg 13, line 3-6, describe making a chimeric molecule similar to those described hereinabove for clone 4, Fig. 1 and 2, which are limited to four types of chimeric molecules, "two are the dimers obtained as α/ζ + β/ζ and two are single chain TCR/ζ chimeric molecules analogous to those in Figure 1

> herein" (pg 8, lines 7-9). In determining whether the phrase has support, it cannot be determined which is the "recovered" portion in Fig. 1. Merely fusing α/β chain variable regions "together" as broadly encompassed by the phrase does not have support in Fig. 1. [P. 3.]

Applicants respectfully traverse the rejection, but have amended step e of claim 1 in the interest of speeding prosecution, both with respect to the Examiner's remarks under §112, first paragraph, and with respect to the Examiner's remarks under §112, second paragraph. As noted *supra*, additional support for the amendments to step e of claim 1 can be found, e.g., on page 6, lines 15-17; on page 12, lines 14-15; in Figures 1-3; and in the Examples, particularly in Example 3.

These passages have been discussed, *supra*, with respect to the preamble, and the same remarks apply here. The Examiner's attention is directed to Figure 1, showing two examples of scTCRs, each having one α chain segment and one β chain segment.

With respect to claim 22, the Patent Office alleges:

> Limiting the variable region of the α/β chain to any "functional" variable region (claim 22) does not have support in the specification as originally filed. Support cannot be found on pg 3, lines 3-22, pg 4, line 1-4, pg 5, line 26, through pg 6, line 7; pg 6, lines 16-20, pg 6, line 23-pg 7, line 25, pg 8, line 3-6, Fig. 13, or the Examples. It was well known in the art at the time of filing that the process of cloning was not limited to isolating nucleic sequences encoding variable regions of TCRs specific for the antigen of interest. Limiting the CTL to having any "functional" variable chain α/β chain does not have support. [P. 4.]

Applicants respectfully traverse the rejection, but have amended claim 22 in the interest of speeding prosecution, both with respect to the Examiner's remarks under §112, first paragraph, and with respect to the Examiner's remarks under §112, second paragraph. As noted *supra*, additional support for the amendments to claim 22 can be found, e.g., on page 5, lines 23-28; from page 12, line 22, to page 13, line 2; in Figures 9-10; and in the Examples, particularly in Example 3.

In addition to the support found at lines 23-28 on page 5 and from line 22 of page 12 to line 2 of page 13, the support for the preamble, as discussed *supra*, also applies here. With respect to the retention of HLA restriction and TAA-specificity, the Examiner's attention is respectfully directed to Figures 9-10 and Example 3, also described *supra*.

Applicants respectfully submit that the amendments to claims 1 and 22 address all of the points made by the Examiner, *supra*, and place claims 1-5 and 22 in a condition for allowance.

V. Rejection of Claims 1-5 and 22 Under 35 U.S.C. §112, Second Paragraph, is Traversed, but Accommodated

The Examiner has rejected claims 1-5 and 22 under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants respectfully traverse the Examiner's rejection.

The Patent Office alleges:

> The preamble of claim 1 remains indefinite because the phrase "prepare... ...a nucleic acid sequence encoding at least one of each of the variable regions of the α and β chains" remains indefinite. The claim fails to set forth the structure of the nucleic acid sequence prepared by stating it comprises a nucleic acid sequence of an α chain TCR and a nucleic acid sequence of a β chain TCR. As written, it appears the claim may encompass a nucleic acid molecule encoding each of the possible α chains and each of the possible β chains. It appears as though applicants are attempting to claim making a nucleic acid sequence encoding each of the numerous α chain variable regions of a TCR and each of the numerous β chain variable regions of a TCR. It appears as though applicants are attempting to limit the α chain and β chain to an α chain and β chain isolated from one particular TCR; however, in reality, the α chain may be from one TCR and the β chain may be from another. The method should result in isolating a nucleic acid sequence comprising a variable region of a TCR α chain and a variable region of a TCR β chain. [Pp. 4-5.]

Applicants respectfully traverse this rejection. As noted in the Amendment filed 26 June 2002,

> With respect to claim 1..., the featured nucleic acid encodes at least one of each of the variable regions of the α and β chains. That is, the nucleic acid must include one of the α chain variable regions and one of the β chain variable regions. [Amendment (6/26/02), page 4.]

The same remarks continue to apply to claim 1, both before and after the present amendment. Claims 2-5 are dependent on claim 1.

The Patent Office alleges:

> Claim 1, step b, as newly amended is indefinite because "said HLA restricted CTL, which contain a nucleic acid molecule comprising a nucleic acid sequence of a variable region of the α chain of the TCR and a nucleic acid sequence of a variable region of the β chain of the TCR" lacks antecedent basis. The previous mention of an HLA restricted CTL was not so limited as in step b. It is unclear if the phrase in step b) -- "which contain..."-- is intended to further limit the HLA restricted CTL produced in step a (in which case, the limitation should be in step a), if the phrase is intended to limit the TCRs that are "specific for said TM" in step a (in which case, the limitation should be in step a) or if the phrase is intended to limit how the CTL are recovered. it is unclear if the phrase "which contain a nucleic acid molecule comprising..." in step b is intended to further describe the TCR of step a) as having an α and β chain, which does not make sense because all TCR have an α and β chain, or if the phrase is intended to further describe nucleic acid sequences cloned in step c) (i.e. cloning a nucleic acid sequence encoding a TCR α chain variable region from the HLA restricted CTL recovered in step b; and cloning a nucleic acid sequence encoding a TCR β chain variable region from the HLA restricted CTL recovered in step b). Clarification is required. [P. 5.]

Applicants respectfully traverse this rejection. Both before and after the present amendment, step a described "immunizing a transgenic non-human mammal species, which produces human HLA, with an effective amount of said TAA to produce HLA restricted cytotoxic T lymphocytes (CTL)." This language provided the necessary antecedent basis. To further the prosecution of the case, however, Applicants have amended the language of step a to provide additional antecedent basis.

The Patent Office alleges:

> Claim 1, step c, as newly amended is indefinite as a whole because the wording of the step is so confusing and does not clearly set forth what nucleic acid sequences are being cloned or from where the nucleic acid sequences being cloned are isolated. In particular, the phrase "said nucleic acid molecule comprising [sic] nucleotide sequence isolated from the HLA restricted CTL, and encoding..." in claim 1, step c, lacks antecedent basis in claim 1, step b, which requires a "nucleic acid molecule comprising a nucleic acid sequence of a variable region of..." The step does not clearly set forth cloning an α chain variable region of a TCR and β chain variable region of a TCR on the HLA restricted CTL recovered in step b. It is unclear if appears applicants are attempting to further describe the nucleic acid molecule of step b or if applicants are attempting to describe the nucleic acid sequences cloned in step c. [Pp. 5-6.]

Applicants respectfully traverse the rejection. To further the prosecution of the case, however, Applicants have amended the language of step c.

The Patent Office alleges:

> Claim 1, step d, as newly amended is indefinite because it is unclear if both the α and β chains are recovered. The phrase said TCR receptor-encoding nucleic acid molecules" lacks antecedent basis. Literal support for the phrase "TCR receptor-encoding nucleic acid molecules" is required when using "said". In addition, use of "TCR" and "receptor" together is redundant because the R in TCR stands for receptor. It is unclear if the phrase "recovering said TCR receptor encoding nucleic acid molecules" refers to recovering the nucleic acid sequence encoding an entire TCR coding region or just the α and β chain variable regions. [P. 6.]

Applicants have eliminated "receptor" following "TCR," but otherwise respectfully traverse the rejection. To further the prosecution of the case, however, Applicants have amended the language of step d.

The Patent Office alleges:

> Claim 1, step e, as newly amended is indefinite because it is unclear whether "fusing the recovered TCR receptor-encoding nucleic acid molecules" refers to fusing a TCR coding region to another TCR coding region or is limited to fusing a α chain variable region to some other TCR coding regions to make a complete α chain, or to

fusing the nucleic acid sequence encoding the α chain variable region to the nucleic acid sequence encoding the β chain variable region. The phrase "fusion protein, which comprises a variable region of the TCR α chain fused to a variable region of the TCR β chain" does not make sense because fusing a nucleic acid sequence encoding variable region of an α chain TCR with a nucleic acid sequence encoding a variable region of a β chain TCR would not result in a functional TCR; an α variable region and a β chain variable region in one protein is not part of the invention. It is unclear if the phrase is intended to limit the fusion proteins to only the single chain TCR described in the specification on pg 8, line 10-11, Fig. 1, ζ-scTCR and ζ-CD8-scTCR, or if the phrase encompasses any of the single chains that make up the dimer TCRs described on pg 8, lines 9-11 (ζ-Vα, ζ-CD8-Vα or ζ-CD8-Vβ described in Fig. 1). [Pp. 6-7]

Applicants respectfully traverse this rejection. To further the prosecution of the case, however, Applicants have amended the language of step e. Again, as noted in the Amendment filed 26 June 2002,

With respect to claim 1..., the featured nucleic acid encodes at least one of each of the variable regions of the α and β chains. That is, the nucleic acid must include one of the α chain variable regions and one of the β chain variable regions. [Amendment (6/26/02), page 4.[

The same remarks continue to apply to claim 1, both before and after the present amendment. Claims 2-5 are dependent on claim 1.

The Patent Office alleges:

New claim 22 is indefinite. It cannot be determined whether the phrase "wherein the variable region of the TCR α chain of step e" is limiting the variable region of the TCR α chain of step e to i) only α chain variable regions that function prior to being in the fusion protein or ii) α chain variable regions that function while in the fusion protein. The phrase regarding the β chain is rejected for the same reason. It is unclear if the "function" in claim 22 is limited to the ability to recognize TAA or if the "function" encompasses any function. The phrase "the variable region of the TCR" in claim 22 is unclear because it is unclear if the phrase refers to the variable region of the TCR in step b) or c) or e). it is unclear when the variable region must be functional. It is unclear what function the variable region must possess. [P. 7.]

Applicants respectfully traverse the rejection. To further the prosecution of the case, however, Applicants have amended the language of claim 22.

While Applicants respectfully disagree with each position of the Examiner, in order to further prosecution in a timely manner, Applicants submit that the amendments to claims 1 and 22 address all of the points made by the Examiner, *supra*, and place claims 1-5 and 22 in a condition for allowance. Support for these amendments has been outlined, *supra*.

VI. Examiner's Withdrawal of Rejection of Claims 1-5 Under 35 U.S.C. §103(a)

Applicants thank the Examiner for withdrawing the rejection of claims 1-5 under 35 U.S.C. §103(a).

CONCLUSION

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

In view of the foregoing amendments and remarks, the present application is respectfully considered in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

Applicants hereby request a one-month extension of time for the Amendment and submit the requisite fee herewith. If, however, a petition for an additional extension of time is required, then the Examiner is requested to treat this as a conditional petition for an additional extension of time. Although it is not believed that any fee is required, in addition to the fee submitted herewith, to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

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